Letters to the Editor

OSELTAMIVIR USE IN PSYCHIATRIC INPATIENTS TAKING CLOZAPINE: EFFECT ON NEUROPSYCHIATRIC EVENTS

DEAR EDITOR:

The pandemic H1N1 influenza was widespread across the world in 2009, increasing patient mortality, morbidity, and healthcare costs significantly. Oseltamivir, effective in decreasing severity and duration of symptoms of influenza types A and B, is generally safe and well-tolerated, with nausea and vomiting being its most common side effects. However, there have been post-marketing reports of neuropsychiatric events (primarily in children and adolescents in Japan) with the use of oseltamivir, and many authorities advise against oseltamivir use, especially in patients less than 21 years of age and those of any age with mental illness.[1]

These post-marketing reports suggest a possible relationship between oseltamivir use and neuropsychiatric events. A United States Food and Drug Administration (FDA) review of clinical trials concluded there was insufficient evidence to confirm that neuropsychiatric events are caused by oseltamivir use. A retrospective cohort study concluded there was no increase in neuropsychiatric events in influenza patients treated with oseltamivir.[2]

The pharmacological mechanism of oseltamivir on neuropsychiatric events is not known, although studies suggest an association between neuropsychiatric events and a change in neurotransmission.[1] Yoshino et al[1] concluded that oseltamivir increased dopamine release in the medial prefrontal cortex (mPFC) of rats and suggested this change in neurotransmission may explain the abnormal behavior in people taking oseltamivir.

Alternatively, neuropsychiatric exacerbation could occur due to influenza itself in the absence of oseltamivir. Beginning in the mid-1990s, many reports originating primarily from Japan described a syndrome of influenza-associated encephalitis occurring in children. Typical symptoms of influenza-associated encephalitis include rapid onset of fever, convulsions, altered consciousness, hallucinations, delirium, motor paralysis, and sensory loss.[3,4] These influenza-associated neuropsychiatric events were reported before oseltamivir was approved for treating influenza.[3]

An area of concern is the potential for neuropsychiatric impacts for the vulnerable population of those who already experience neuropsychiatric symptoms and take oseltamivir. Most likely to be destabilized psychiatrically would be those whose psychiatric history includes a serious and persistent mental illness (SPMI) with symptoms refractory to conventional treatment. Hospitalized patients receiving clozapine would be one such vulnerable population.

The objective of this retrospective chart review was to gain further clinical knowledge and contribute to the literature by evaluating the effect of oseltamivir on the neuropsychiatric events of psychiatric inpatients taking clozapine. Patients taking clozapine were selected for this study as they tend to be more psychiatrically vulnerable and thus may demonstrate more readily measurable behavioral disruptions.

A retrospective chart review was conducted on the records of 31 psychiatric patients at a state psychiatric center who received both clozapine and oseltamivir. The sample comprised patients 18 years

TABLE 1. PRN prescribed frequency

TYPE OF DRUG	TIME PERIOD 1	TIME PERIOD 2
NSAID	1	0
Acetaminophen	4	1
Antipsychotic	2	0
Anxiolytic	2	0
Insomnia	3	0
Antihistamine	1	0
Antibiotic	0	1
Other (Constipation/ furosemide)	2	0

KEY: PRN=*pro re nata*; NSAID=nonsteroidal anti-inflammatory drug

TABLE 2. STAT medication use

TYPE OF DRUG	TIME PERIOD 1	TIME PERIOD 2
NSAID	1	0
Acetaminophen	4	1
Antipsychotic	0	1
Anxiolytic	7	0
Insomnia	1	0
Antihistamine	3	0
Antibiotic	1	0
Other (constipation/ furosemide)	6	1

KEY: STAT=*statim*; NSAID=nonsteroidal anti-inflammatory drug

TABLE 3. Psychiatric events

TYPE OF DRUG	TIME PERIOD 1	TIME PERIOD 2
Violence	6	3
Anxiety	5	0
Self-violence	9	0
Compulsive behavior	2	0
Attention seeking	3	0

old or older who were inpatients between 1/1/06 and 4/30/06 and who received both clozapine and oseltamivir during an inpatient stay between 3/1/06 and 4/30/06. Data pertaining to the primary measure of the study (whether the use of oseltamivir contributes to neuropsychiatric events) were collected for each of the 31 patients.

The *pro re nata* (PRN) and *statim* (STAT) medication use of 31 patients were evaluated for frequency. Data analysis determined the difference in PRN prescribed frequency before and after oseltamivir was statistically significant at 0.003 (p=0.05) in that there was higher use before oseltamivir (Table 1). The difference between before and after for STAT medication use was also statistically significant at 0.028 (p=0.05), again before oseltamivir (Table 2). The occurrence of psychiatric events recorded before and after oseltamivir was also statistically significant at 0.024 (p=0.05) with more events occurring before the use of oseltamivir (Table 3). Our results did not support oseltamivir having any impact on neuropsychiatric status.

A potential limitation to this study is that all subjects were already stabilized on an antipsychotic medication. Additional limitations include a small sample of 31 inpatients is likely not an adequately robust sample from which we can generalize our results. Further, the variables vital signs, Brief Psychiatric Rating Scale (BPRS), and Global Assessment of Functiong (GAF) scores could not be included in the results as these variables were not consistently collected at a time correlated to oseltamivir use. Objective ratings with reliable and well-validated scales of symptom severity and global functioning would have strengthened our study. Our results were based on review of individual patient records, not on face-to-face evaluation. Misfiling, illegibility, incomplete records, and clinicians' poor articulation of the subjects' symptoms could all contribute to data distortion.

Further work in this direction is planned by the authors, including a retrospective chart review of all inpatients who received oseltamivir, in order to increase the sample size to more than 200 subjects while broadening the demographics of our sample.

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With regards,

Shari N. Allen, PharmD; Tammie Lee Demler, PharmD, MBS, BCPP; Eileen Trigoboff, RN, DNS; and Lewis A. Opler, MD, PhD

All from the Buffalo Psychiatric Center State University of New York, University at Buffalo School of Pharmacy and Pharmaceutical Sciences, New York State Office of Mental Health, Buffalo, New York

Address correspondence to: Shari N. Allen, PharmD, 400 Forest Ave., Buffalo, NY 14213; Phone: (716) 816-2438; Fax: (718) 816-2496; E-mail: Shari.Allen@omh.state.ny.us

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